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Gene Section
Review

MYO1A (myosin IA)

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Abstract

Review on MYO1A, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: BBMI, DFNA48, MIHC, MYHL

HGNC (Hugo): MYO1A

Location: 12q13.3

Note

Orientation: minus strand.

DNA/RNA

Description

There are several transcripts described for MYO1A. The two transcripts better characterized contain 28 and 29 exons spanning over 21 kb and both code for an identical protein of 1043 amino acids.

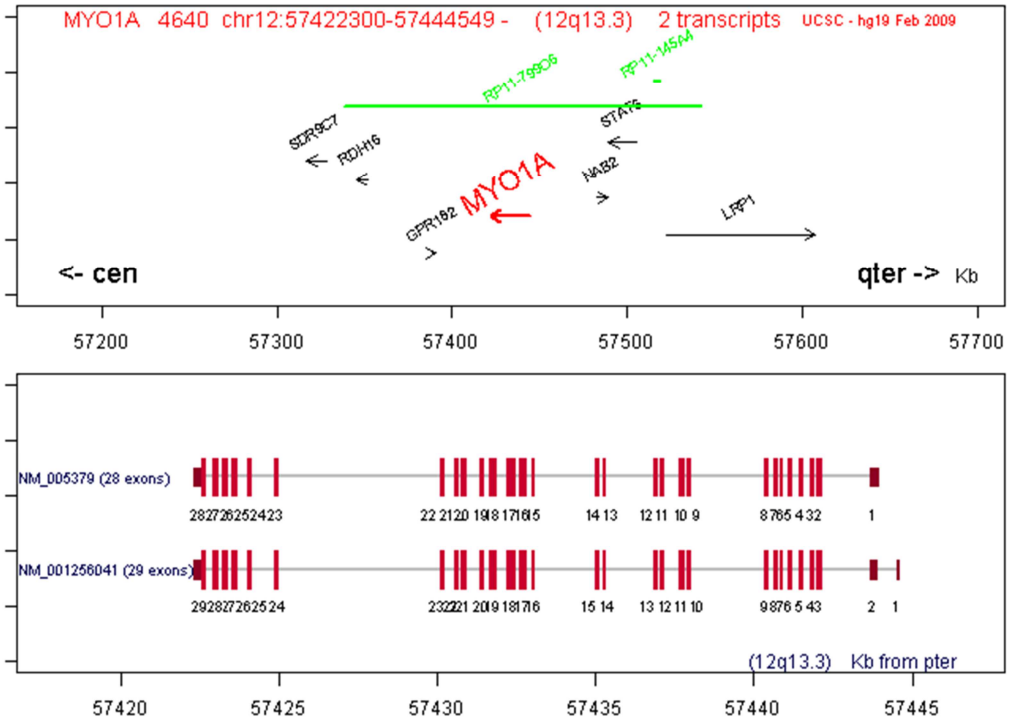

Figure 1. Diagram of DNA/RNA.

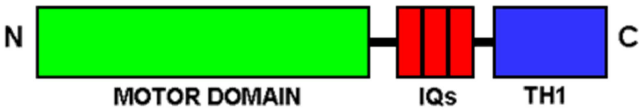

Figure 2. Protein structure of MYO1A.

Protein

Description

The protein encoded by the MYOSIN-IA gene belongs to the myosin superfamily.
Like all myosin-1 isoforms, MYO1A contain these three core domains (figure 2): an N-terminal motor domain that coordinates ATP hydrolysis with actin binding and force generation; a central neck region made up of varying numbers of IQ motifs, which bind calmodulin or calmodulin-like proteins; and a tail region, which includes a highly basic C-terminal tail homology 1 (TH1) domain that is responsible for membrane binding (Coluccio and Bretscher, 1990; Krendel and Mooseker, 2005; McConnell and Tyska, 2010; Nambiar et al., 2010).

Expression

Myo1a is highly expressed in the enterocytes that line the mucosa of the small intestine (Matsudaira and Burgess, 1979; Skowron and Mooseker, 1999). Expression of MYO1A has also been observed at relatively high levels in gastric epithelium when compared to other organs such as endometrium, myometrium, ovary and prostate (figure 3).
In tumor samples, MYO1A mRNA expression in human gastric adenocarcinomas is comparable to intestinal adenocarcinomas, and significantly higher than in other tumor types (Mazzolini et al., 2013) (figure 4).
Myo1a transcripts are also present in rodent inner ear at low level (Dumont et al., 2002).

Localisation

Myo1a localizes to the cellular membrane through to the C-terminal tail domain.
In the enterocytes that line the mucosa of the small intestine, MYO1A localizes to the apical brush border membrane (Matsudaira and Burgess, 1979; Collins and Borysenko, 1984; Skowron and Mooseker, 1999) (figure 5).

Function

Myosin Ia (MYO1A) is a major component of the cytoskeleton that underlies and supports the apical brush border of the enterocytes.
MYO1A forms a spiral array of bridges that links the microvillar actin core to the membrane (Chantret et al., 1988; West et al., 1988; Beaulieu et al., 1990).
Here, Myosin-1a plays a critical role in maintaining the brush border composition, structure, and regulating the microvillar membrane tension (Tyska et al., 2005; Nambiar et al., 2009), Myo1a also plays a role in powering the release of vesicles from the tips of the microvilli (McConnell et al., 2009).

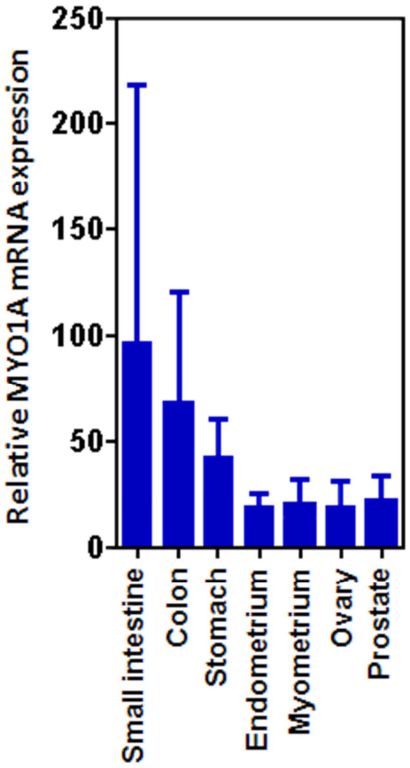

Figure 3. Relative MYO1A mRNA levels in human normal tissues. MYO1A mRNA levels in human normal and tumor samples were obtained from a collection of 667 normal human samples from different tissues (Gene Expression Omnibus: GSE7307) and 10000 normal and tumor samples from GeneSapiens.org (Kilpinen et al., 2008).

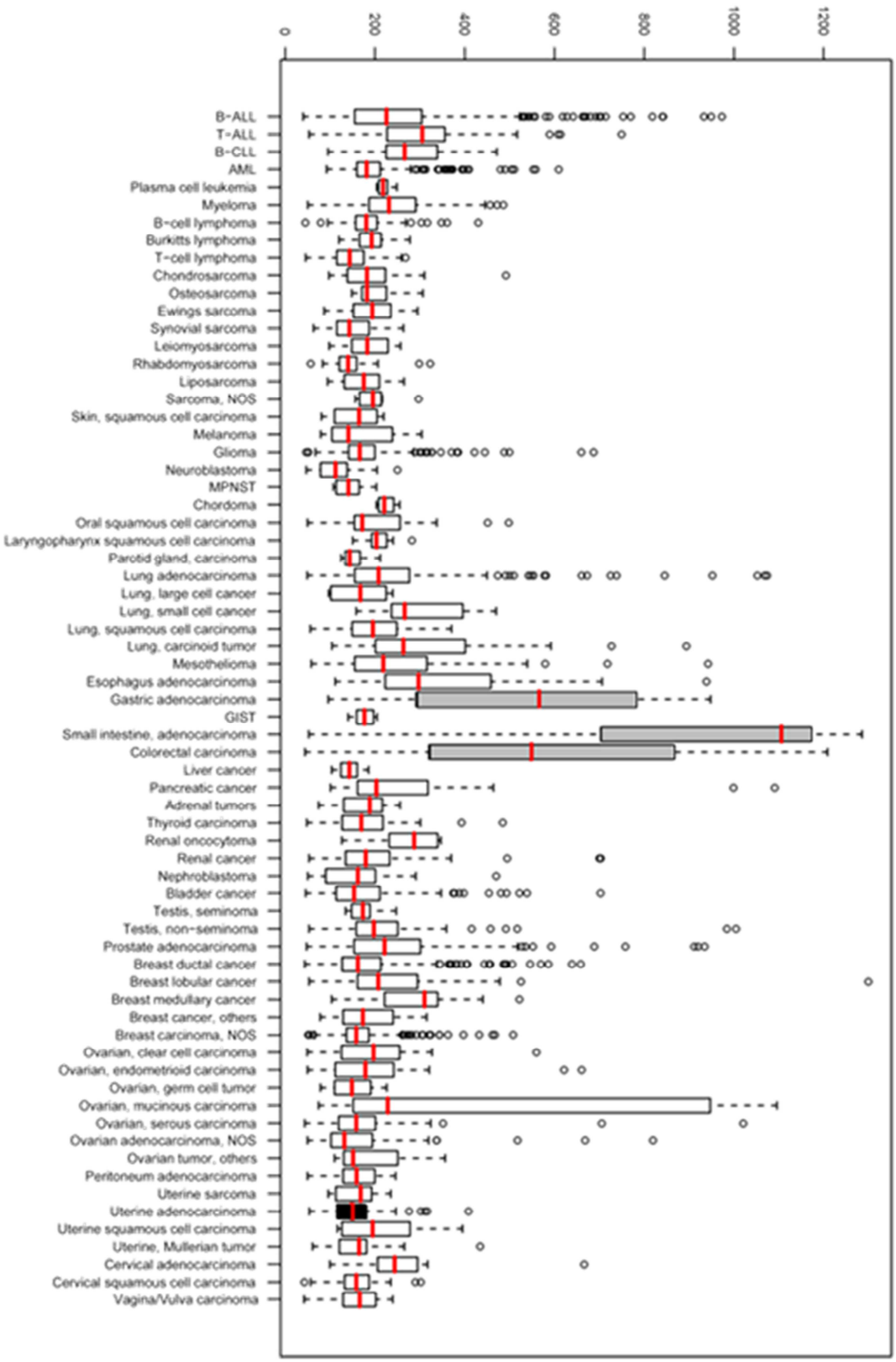

Figure 4. Relative MYO1A mRNA levels in human tumors of different origin. Box-whisker plot of the gene's expression in cancer tissues. The bottom of the box is the 25th percentile of the data, the top of the box is the 75th percentile, and the vertical red line is the median. The whiskers extend to 1.5 times the interquartile range from the edges of the box, and any data points beyond this are considered outliers, marked by hollow circles. Filled grey bars are gastrointestinal carcinomas.

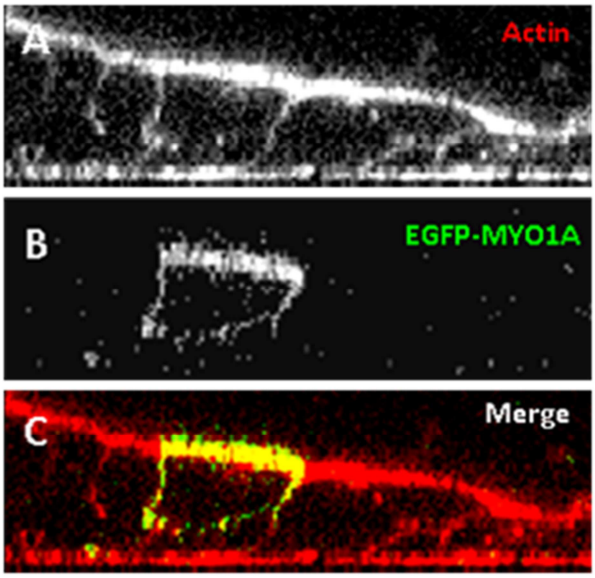

Figure 5. *MYO1A localizes to the apical membrane of intestinal epithelial cells. MYO1A-GFP was transfected into the colon cancer cell line Caco-2. The image was taken by confocal microscopy and represents an orthogonal stuck of a monolayer of cells. (A) Actin staining with rhodamine-phalloidin shows the apical and baso-lateral membtanes of the cells. (B) EGFP-MYO1A localizing in the apical membrane. (C) Overlay (modified from Mazzolini et al., 2012).*

Mutations

Germinal

The following germinal mutations have been reported in eight unrelated patients coming from central and southern Italy and affected by sensorineural bilateral hearing loss of variable degree: one nonsense mutation, one trinucleotide insertion leading to an additional amino acid, and six missense mutations (Donaudy et al., 2003) (table 1).

Somatic

Mazzolini et al. reported frequent frame-shift somatic mutations in colorectal and gastric cancer. These mutations were found with the following frequencies: 44,4% (16 of 36) in microsatellite-instable colorectal cancer cell lines; 31,3% (42 of 134) in primary colon tumors; 46,8% (22/47) in gastric microsatellite-instable primary tumors. No mutations were observed in the matching healthy intestinal mucosa.

All the mutations observed were insertions or deletions in an A8 microsatellite tract located in exon 28. The most frequent mutation is the deletion of one A ($MYO1A^{A7MUT}$). All the mutations found appeared to be heterozygous as the wild type allele was also visible in all cases (figure 6, panel A). The $MYO1A^{A7MUT}$ mutation causes sub-cellular mislocalization (figure 6, panel B) and decreased stability of Myosin-1a (Mazzolini et al., 2012; Mazzolini et al., 2013). Additional mutations have been found in colorectal tumors without microsatellite instability (TCGA; figure 6, panel C).

Exon	Nucleotide	Amino Acid
3	277C/T	R93X
4	349-350A	349-350 insCTT
10	916G/A	V306M
12	1155G/T	E385D
18	1985G/A	G662E
18	2021G/A	G674D
22	2390C/T	S797F
25	2728T/C	S910P

Table 1. MYO1A mutations related to sensorineural bilateral hearing loss (Donaudy et al., 2003).

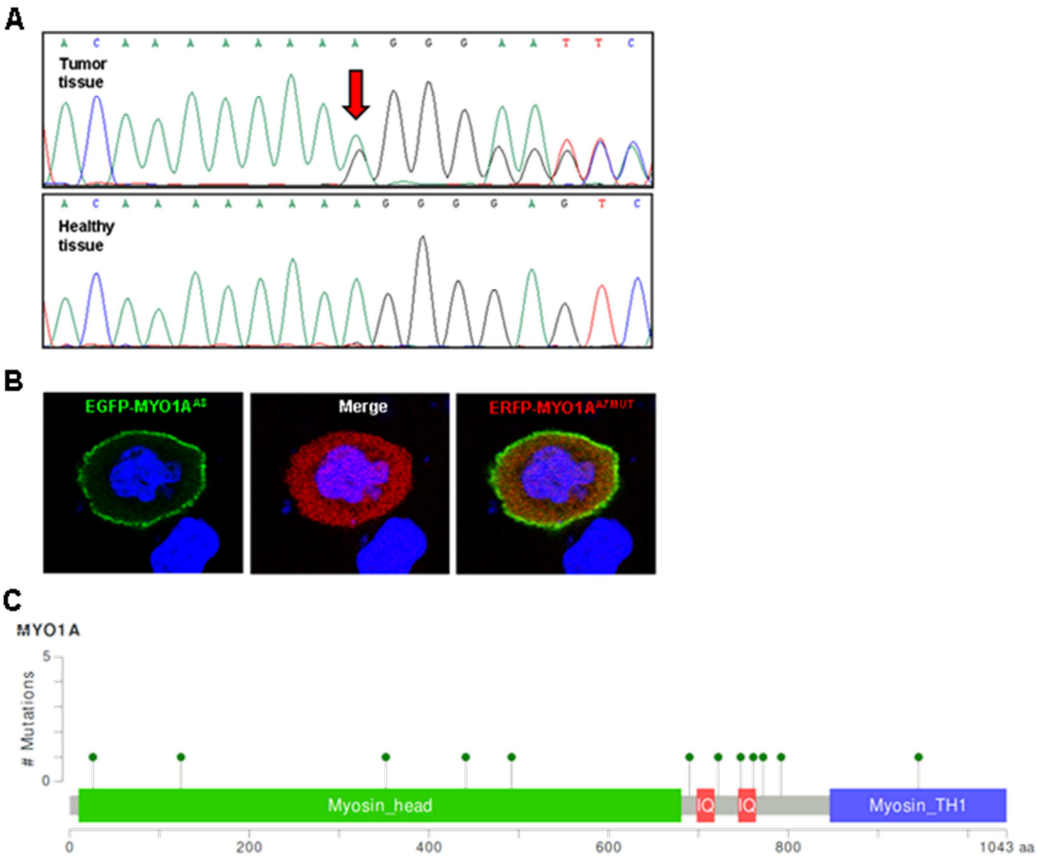

Figure 6. Somatic mutations of MYO1AA7MUT. (A) Frameshift mutations in the A8 track in Exon 28 of MYO1A. (B) Co-transfection of wild type EGFP-MYO1Awt and mutant ERFP-MYO1AA7MUT demonstrated that the mutant protein mislocalized to the cytoplasm of undifferentiated Caco2 cells (modified from Mazzolini et al., 2012). (C) Localization of additional mutations found in colorectal tumors without microsatellite instability.

Implicated in

Colorectal cancer

Note

The brush border protein Myosin Ia (MYO1A) has been demonstrated to be important for polarization and differentiation of colon cancer cells and is frequently inactivated in colorectal tumors by genetic and epigenetic mechanisms. Mazzolini et al. reported MYO1A frame-shift mutations in 32% (37 of 116) of the colorectal tumors with microsatellite instability. Evidence of promoter methylation was observed in a significant proportion of colon cancer cell lines and primary colorectal tumors.

The loss of polarization/differentiation resulting from MYO1A inactivation is associated with higher tumor growth in soft agar and in a xenograft model. In addition, the progression of genetically and carcinogen initiated intestinal tumors was significantly accelerated in Myo1a knockout mice compared with Myo1a wild-type animals. Moreover, MYO1A tumor expression was found to be an independent prognostic factor for colorectal cancer patients. Patients with low MYO1A tumor protein levels had significantly shorter disease-free and overall survival compared with patients with high MYO1A (logrank test P = 0.004 and P = 0.009, respectively).

The median time-to-disease recurrence in patients with low MYO1A was 1 y, compared with >9 y in the group of patients with high MYO1A. These results identified MYO1A as a tumor-suppressor gene in colorectal cancer and demonstrate that the loss of structural brush border proteins involved in cell polarity are important for tumor development (Mazzolini et al., 2012).

Gastric cancer

Note

Frame-shift somatic mutations have been reported in 46,8% (22/47) of gastric microsatellite-instable primary tumors. Frequent MYO1A promoter hypermethylation was also found in gastric tumors (Mazzolini et al., 2013).

Endometrial cancer

Note

Rare mutations have been reported in 6,2% (3/48) of endometrial microsatellite-instable primary tumors (Mazzolini et al., 2013). The low frequency of this mutation in endometrial tumor is likely to

reflect the background mutation rate occurring in endometrial MSI tumors.

Nonsyndromic hearing loss

Note

MYO1A, which is located within the DFNA48 locus, was the first myosin I family member found to be involved in causing deafness and may be a major contributor to autosomal dominant-hearing loss. Several mutations in the MYO1A gene were found to be associated with hearing loss (table 1) (Donaudy et al., 2003). In particular, the substitution E385D has been characterized to disrupt the mechanochemical coupling and subcellular targeting of Myosin-1a (Yengo et al., 2008).

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